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(57) Abstract

Described here are a novel means and device for noninvasively quantifying important blood constituents. Total hemoglobin, arterial oxygen content, hematocrit, and other parameters can all be determined quickly and easily without the need for skin puncture or lengthy laboratory analysis. The invention described here concerns the simultaneous measurement or control of volume changes and changes in the mass of either oxyhemoglobin, total hemoglobin, or reduced hemoglobin or other blood constituents such as glucose, bilirubin or cholesterol. The data obtained by these measurements is used to quantify the parameters of interest.

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DESCRIPTION

METHOD FOR NONINVASIVE INTERMITTENT AND/OR CONTINUOUS HEMOGLOBIN, ARTERIAL OXYGEN CONTENT, AND HEMATOCRIT DETERMINATION

Cross-Reference to a Related Application

This application is a continuation-in-part of our co-pending application Serial No. 08/052,806, which was a continuation of Serial No. 07/864,883, which was a divisional of our application Serial No. 07/368,636, now U.S. Patent No. 5,101,825, which was a continuation-in-part of our application Serial No. 07/264,119, filed October 28, 1988, now abandoned.

Background of the Invention

Arterial oxygen content was once assessed relying only on physical signs and symptoms such as cyanosis, tachypnea, bradycardia, tachycardia, dyspnea, and shortness of breath. Today, devices exist which allow accurate and rapid quantitative measurement of arterial oxygen content. Partial pressure of oxygen (PO_2) in blood, percent hematocrit (Hct), percent arterial hemoglobin saturation (SaO_2), gram-percent total hemoglobin (THb), and arterial oxygen content (CaO_2) are all readily available to the physician in modern hospitals.

Unfortunately, however, measurement of these variables has until recently always required an invasive arterial puncture or phlebotomy. Once the whole blood sample is obtained, analysis is accomplished using spectrophotometric and chemical means.

During the early 1970's, the first pulse oximeter was introduced. This device permitted approximation of SaO_2, termed SpO_2, by noninvasive means. The design was subsequently improved upon and the current generation of pulse oximeters is now commonplace in the intensive care unit (ICU), emergency room (ER), operating room (OR), and recovery room (RR).

Pulse oximeter design is well documented. It utilizes two light-emitting diodes (LED). Each LED emits a specific wavelength of light that is transmitted through the tissues to a photodetector. These wavelengths are chosen to be around 660 nm (red spectrum) and around 940 nm (near-infrared spectrum) because of the absorbency characteristics of oxyhemoglobin (HbO_2) and reduced hemoglobin (RHb). An electrical signal consisting of two components is generated by the photodetector receiving the LED emission. There is an invariant direct current (DC) component to the signal which represents ambient background light and transmission of light through invariant, that is, nonpulsatile tissues such as skin, bone, and, to a certain extent, veins. The second component

of the signal is an alternating current (AC) which represents the varying transmission of light through the pulse-varying tissues, i.e., the arteries and capillaries. Both the AC and DC components are affected by altered LED light intensity. The AC signals must be corrected for inter-LED light intensity differences prior to their use for SpO_2 calculation. A pulse oximeter does this by dividing each LED's AC signal by its corresponding DC signal to produce the "corrected" or "normalized" AC signal. The terms "corrected" and "normalized" are used synonymously herein when referring to this procedure. The ratio of the corrected AC signal at 660 nm to that at 940 nm is compared to a stored calibration curve that yields SpO_2. Thus, to calculate SpO_2, a pulse oximeter generates a corrected AC signal for both LED wavelengths.

At this time, determination of the other variables, such as methemoglobin (MetHb), Hct, THb, CaO_2, continues to require arterial puncture or phlebotomy. Skin puncture procedures are painful to the patient, time consuming, and provide opportunities for infection. There is a great need for a rapid and accurate noninvasive means of assessing THb, CaO_2, and Hct. Such an assessment means would enable the health care provider to quickly evaluate and follow a patient's circulating blood status. Questions of hemodilution during volume expansion in the field, ER, ICU, and OR would be rapidly answered. Hemoconcentration after blood transfusion, hemodialysis or bone marrow transplantation could be followed without repeated venipuncture. Furthermore, many "routine" screening phlebotomies to assess THb and Hct such as for preoperative laboratory studies in children and adults could be eliminated.

Brief Summary of the Invention

The subject invention concerns a novel means and device for noninvasive determination of total hemoglobin, arterial oxygen content, and hematocrit. Advantageously, these determinations can be made intermittently and/or continuously. The novel procedure described here is painless and eliminates the need for skin punctures. It is cost effective because there is no need for needles, syringes, gloves, bandages, or skilled technicians. Advantageously, critical data can be obtained in seconds rather than minutes or hours and continuously rather than episodically.

The determination of the blood parameters of interest is accomplished by measuring the change in the mass of hemoglobin (HbO_2, RHb, or THb) resulting from a measured or controlled change in volume of blood. Each of these two measurements or controlled changes can be achieved noninvasively. For example, the change of mass of hemoglobin species associated with a controlled change in volume can be measured photometrically by passing light of appropriate wavelength(s) through a portion of the body. The attenuation of the light which can be detected by a photometer is related to the amount of hemoglobin species in the blood being analyzed. When changes occur

in the volume or hemoglobin species concentration of blood being analyzed, corresponding changes in the mass of hemoglobin species can be measured. There are several noninvasive means which can be used to measure or control changes in blood volume in the portion of the body being analyzed.

Once these measurements have been made, the blood parameters of interest can be readily calculated.

Brief Summary of the Figures

Figure 1 is a schematic representation of one embodiment of the invention where HbO_2 is measured directly and a pulse oximeter is utilized.

Figure 2 is a schematic representation of one embodiment of the invention where HbO_2 is measured directly and a pulse oximeter is not explicitly incorporated.

Figure 3 is a schematic representation of one embodiment of the invention where THb is measured directly and a pulse oximeter is not explicitly incorporated.

Figure 4 is a schematic representation of one embodiment of the invention where desired hemoglobin species is/are measured and a pulse oximeter is not explicitly incorporated.

Figure 5 is a diagram of the Caliper-mounted device for collection of dog data.

Figure 6 is dog data total hemoglobin (g/dL) versus $\ln(V_o/V_1)$/Del-X (mm^{-1}).

Figure 7 is a diagram of the device used for collecting human data.

Figure 8 is data of human population total hemoglobin (g/dL) versus $\ln(V_o/V_1)$/Del-X (mm^{-1}).

Figure 9 is a data collection device.

Detailed Description of the Invention

Oxygen content in arterial blood can be calculated using the formula:

$$CaO_2(mL\ O_2/dL) = THb(g/dL) \times SaO_2 \times 1.39(mL\ O_2/g\ HbO_2), \quad (1)$$

where SaO_2 is a fraction (HbO_2/THb). Oxyhemoglobin (HbO_2) is the oxygen carrying species of THb and can be calculated,

$$HbO_2(g/dL) = THb \times SaO_2. \quad (2)$$

Substituting Equation (2) into Equation (1),

$$CaO_2(mL\ O_2/dL) = HbO_2(g/dL) \times 1.39(mL\ O_2/g\ HbO_2). \quad (3)$$

It becomes apparent that oxygen content can be calculated if oxyhemoglobin is known. Therefore, if the mass of oxyhemoglobin molecules [$mHbO_2(g)$] in a given volume [V(dL)] is known, the oxygen content of that volume can be determined. Stated another way, if a change in the $mHbO_2$ can be measured along with the corresponding change in volume, oxygen content can be measured. This relationship can be written

$$HbO_2(g/dL) = [mHbO_{2_{t2}} - mHbO_{2t1}]/[V_{t2} - V_{t1}], \quad (4)$$

where subscripts t1 and t2 represent two points in time. This can be rewritten as

$$HbO_2 = \Delta mHbO_2/\Delta V, \quad (5)$$

where $\Delta mHbO_2$ is the change in mass of the HbO_2 species and ΔV is the measured corresponding change in volume. The value for $\Delta mHbO_2$, if $mHbO_2$ is measured directly, can be calculated using a signal generated by a pulse oximeter, for example.

$mHbO_2$ can also be determined indirectly. Indirect determination requires accurate SpO_2 and either RHb or THb values. SaO_2 and SpO_2 are known to be close to each other. If RHb and SpO_2 are known, then

$$RHb = THb \times [(100-SpO_2)/100], \quad (6)$$

and solving for THb yields

$$THb = (RHb \times 100)/(100-SpO_2). \quad (7)$$

Substituting equation (7) into

$$HbO_2 = THb - RHb, \quad (8)$$

one obtains:

$$HbO_2 = [(RHb \times 100)/(100 - SpO_2)] - RHb. \quad (9)$$

If THb and SpO_2 are measured, Equation (2) can be utilized for indirect $mHbO_2$ determination and equation (8) will then permit calculation of RHb.

The invention can be practiced utilizing Equations (4) and (5). The same equations may be used for any hemoglobin species, e.g. for THb, using a wavelength of 810 nm. These equations are clinically useful approximations of the pertinent biological phenomena to be measured by the subject invention. Additional terms can be added to Equations (4) and (5). These additional terms reflect the relatively small effects which are attributable to respiration and other physiological activities. These effects can be extracted and utilized for analysis of respiration and other clinically-relevant parameters.

Once $\Delta mHbO_2$ is calculated, completion of the CaO_2 calculation requires determination of ΔV (Eqn. 5). This can be accomplished in numerous ways.

Thus, CaO_2 is calculated in real-time by one of several similar algorithms entirely through noninvasive means. If the algorithm solving directly for $\Delta mHbO_2$ is used, THb can be calculated using the SpO_2 output from another device, such as the pulse oximeter, with the equation

$$THb(g/dL) = CaO_2(mL\ O_2/dL)/[SpO_2 \times 1.39(mL\ O_2/g\ HbO_2)]. \quad (10)$$

Of course, if the light source from a pulse oximeter is used to obtain $\Delta mHbO_2$, then SpO_2 from that same pulse oximeter, or similar device, can be utilized (Figure 1).

Hct can be estimated from either CaO_2 or THb using additional calibration curves. Most commonly, Hct is well approximated by multiplying THb by a factor of three. For example, if a patient has a CaO_2 = 20 mL O_2/dL at SpO_2 = 100% and a THb = 15 g/dL (i.e., 15 gram-percent), one can estimate that with normal red blood cell (RBC) morphology Hct is near 45%. If THb is reduced, a proportional Hct change can be anticipated. If one has prior knowledge of RBC morphology, for example, that the RBC's are macrocytic or microcytic, then this can be entered into the monitor and an appropriate calibration curve used.

The claimed device comprises a small appliance that is easily attached to the patient. For example, the device can be attached onto the finger, earlobe, wrist, lips, nares, tongue, cheek, or some other site. The device further comprises a signal processing part that also displays the results. The device displays CaO_2, THb, and an estimate of Hct continuously or intermittently. Theoretically, MetHb, and Carboxy Hb (COHb), glucose, bilirubin, etc. can also be quantified.

Although SpO_2 input to the device is required for calculation of THb with two of the algorithms, the device does not necessarily require incorporation into a pulse oximeter, or similar device, to determine THb. Instead, an SpO_2 value can be obtained via the digital output port of a pulse oximeter, or similar device, and input into the proposed device. Thus, the device could be incorporated into a pulse oximeter (or similar device), as illustrated in Figure 1, or operate as a unit distinct from it as diagrammed in Figures 2, 3 and 4.

While the measurements for quantitating THb may be conducted by measuring volume changes in illuminated tissues, the signal may be amplified, and individual tissue differences may be reduced, by employing a volume change control means. This embodiment of the invention, including its theoretical basis and practical implementation, are described below. Example 17 provides *in vivo* results obtained using this embodiment of the invention. In addition, the extension of this method to monitoring of other relevant blood constituents, besides hemoglobin, such as glucose, bilirubin or cholesterol, is also described.

Efforts to use nonpulsation photometric methods to measure light absorbing blood constituents and related parameters have all been hampered by the fact that light absorption and optical path length through nonblood tissues differ from person to person and that the optical path lengths through the blood itself are unknown. Pulsation methods like pulse oximetry which can eliminate these factors are generally limited to determining ratios of blood constituents and further limited by the fact that naturally pulsating blood gives a very low signal. This signal, typically measured by photodiode as a time varying (AC) signal superimposed on a large constant (DC) value, is generally only about 1% of the DC value. What is more, AC signal strengths are dependent on tissue perfusion which depends on such things as blood pressure, vascular condition, temperature and blood pressure arm cuff cycling. Blood constituents that do not absorb light as strongly or are of more dilute concentration as the various species of hemoglobin provide even weaker photometric signals. As a result, there remains a need to provide a more sensitive method for measuring these parameters which is less susceptible to noise and inter-individual variations. By measuring or controlling volume changes through tissue compression, this goal is realized.

The theory underlying our tissue compression method for determining THb and other blood constituents *in vivo* is similar to pulse oximetry theory. The compression method differs from pulse

oximetry in that actual concentrations of hemoglobin (or other light absorbing constituents such as glucose, bilirubin or cholesterol) may be determined.

It is reasonable to think of living tissue as being comprised of three compartments that behave differently under compression. The first and most mobile compartment is blood. As tissue is compressed, arterial, venous and capillary blood readily leaves the tissue because it is mobile. This is easily demonstrated by pinching the fingernail bed and observing that it blanches as blood exits the tissue. When pressure is released, the blood quickly returns. The next most mobile compartment is interstitial fluid, trapped within tissue planes and adsorbed to hydrophilic molecules. These fluids migrate out of the tissue at a much slower rate. The third compartment consists of immobile, solid tissues.

In blood, the major light absorbers are species of hemoglobin: RHb, HbO_2, COHb and metHb. COHb typically comprises 3% to 5% of all hemoglobin and as much as 10% to 15% in smokers. MetHb is typically less than 1% of the total except in rare disease states. The remaining hemoglobin is primarily split between RHb and HbO_2, depending on blood oxygen saturation. Not only are extinction coefficients different for each of these species, but the coefficients vary with wavelength of light.

The photometric measurement of blood constituents is described by the Beer-Lambert law in which collimated light travels through a uniform light absorbing medium:

$$\ln(I_1/I_0) = - K C L \qquad (11)$$

where I_0 is the light source intensity as it enters the medium, I_1 is the light intensity emerging from the absorbing medium, K is a proportionally constant called the "extinction coefficient" which describes the characteristics of the substance in the medium that absorbs light, C is the concentration of the light absorbing substance and L is the optical path length through which the light passes. For more than one light absorber in the medium, the equation becomes:

$$\ln(I_1/I_0) = -(K_1 C_1 + K_2 C_2 + K_3 C_3 + \ldots)L_1 \qquad (12)$$

where the numerical subscripts for K and C indicate extinction coefficients and concentrations for light absorbers numbered 1, 2, 3 etc. The optical path length L_1 is assumed to be the same for all absorbers.

Modifying the Beer-Lambert relation in equation (12) for the two light absorbers Hb and HbO_2 gives the relation:

$$\ln(I_1) - \ln(I_0) = -(K_{Hb} C_{Hb} + K_{HbO2} C_{HbO2})L_{B1} - K_T C_T L_T \quad (13)$$

where K_{Hb}, K_{HbO2} and K_T are extinction coefficients for RHb, HbO_2, and nonblood tissues and C_{Hb}, C_{HbO2} and C_T are concentrations of RHb, HbO_2 and the light absorbing substances in the nonblood tissues, respectively. The subscript "1" indicates that measurements are made at a first point in time. Optical path lengths are designated as L_{B1} through blood and L_T through nonblood tissues.

Equation (13) may be duplicated for a second point in time, designated by the subscript "2", at which point the optical path length through the blood is different than at the first point in time:

$$\ln(I_2) - \ln(I_0) = -(K_{Hb} C_{Hb} + K_{HbO2} C_{HbO2})L_{B2} - K_T C_T L_T \quad (14)$$

Note that the only changes from (13) to (14) are that L_{B1} changes to L_{B2} and I_1 to I_2. Subtracting equations (13) and (14) accomplishes three things. First, the light source intensity I_0 is eliminated. Thus, I_0 need not be measured. Second, the last terms of equations (13) and (14) that account for nonblood tissues are also eliminated so that person-to-person differences need not be known. This second item is what makes it possible for our method and device to work on the general population without the need for individual calibration. Third, only the ratio of the variables I_2 and I_1 needs to be known and not their actual values. This means that measurement calibration for actual light intensity is not necessary. The equation that results from the subtraction is as follows:

$$\ln (I_2/I_1) = (K_{Hb} C_{Hb} + K_{HbO2} C_{HbO2})\Delta L_B \quad (15)$$

where $\Delta L_B = (L_{B1} - L_{B2})$.

A simplified model comprises light passing from a source on one side of a volume of living tissue to a detector on the other side. The blood and less mobile nonblood tissues occupy separate and distinct compartments. As the tissue is compressed, the optical path length through blood decreases while the path length through nonblood tissues is unchanged. Thus, the term ΔL_B in equation (15) is due entirely to changes in the blood optical path length. If the actual value of ΔL_B is known, then the only unknown values left in equation (15) are the concentrations of RHb and HbO_2 (i.e., C_{Hb} and C_{HbO2}, respectively).

Using the isobestic wavelength where RHb and HbO_2 absorb light equally (i.e., their extinction coefficients are identical) these two unknowns can be reduced to only one unknown, the concentration of total hemoglobin (C_{THb} or simply THb). This isobestic point occurs at a wavelength of 805 nm. At the isobestic point, the extinction coefficient of COHb is also very small relative to

Hb and HbO_2 so that the resulting value of THb includes the concentrations of these functional hemoglobin species but is not affected by the nonfunctional species COHb. While metHb is a strong absorber at 805 nm., it is present in very low concentrations and will have no appreciable effect on the THb value. With isobestic light, equation (15) becomes:

$$\ln(I_2/I_1) = K_{THb}\, C_{THb}\, \Delta L_B \qquad (16)$$

which can be solved for C_{THb} as follows:

$$THb = C_{THb} = \ln(I_2/I_1) / (K_{THb}\, \Delta L_B) \qquad (17)$$

Since the ratio of I_2 to I_1 is measured, K_{THb} is an empirically determined constant and ΔL_B is measured or controlled by the device that compresses the tissue, THb may be calculated.

Thus, all that is required is that the initial and final light intensities be measured, the constant K_{THb} (or any other blood parameters empirically determined constant) and a known change in the optical path produced by a volume control (tissue compression) means to adjust the separation between the light emitter and detector.

The tissue compression method described here may be used to determine actual blood constituent concentrations instead of just ratios of concentrations like the pulse oximeter does. Since the method involves compressing tissues to change the optical path length through blood, the optical path length change is controlled and not dependent on the variability of natural pulsations, as in pulse oximetry. Thus, large signals on the order to 10% to 40% of the DC value are possible on demand with consequent improvements in signal to noise ratio and accuracy of blood parameter determination. Because of the increased signal strength, the tissue compression method is useful in quantitating other blood constituents that do not absorb light as strongly as or are present in more dilute concentrations than the various species of hemoglobin. The tissue compression method may also be adapted to the use of more than one wavelength of light to quantitate more than one blood constituent.

Accordingly, all of the foregoing considerations may be applied to measurement of blood chromophores having light absorption maxima up to and including 11,000 nm. As a specific example, blood glucose may be measured according to the above described theoretical considerations using at least one wavelength, for example, 9,700 nm. Since measuring blood glucose is difficult due to its weak light absorption characteristics and its dilute concentration in the blood, glucose determination may require one or more reference wavelengths for its measurement. Matrix algebra

derivations solving for glucose imply that the additional wavelength needed for glucose concentration determination may be any wavelength that accurately measures some other blood constituent - hemoglobin, for instance. What this means is simply that once hemoglobin concentration has been determined from a system using one wavelength, the addition of a second, glucose-sensitive or other blood constituent-sensitive, wavelength allows accurate measurement of glucose or other constituent where it could not do so by itself.

In practical terms, the foregoing theoretical considerations are implemented by a device having the following constituent parts:

A. Photometric Unit - comprising a laser diode or other light emitting source (810 nm, 9700 nm, etc.), for example, filtered, collimated, ultra bright white light sources, and control circuitry, photodiode and signal conditioning circuitry and mounting hardware.

B. Tissue Compression Unit - comprising a mechanical linkage for effecting appropriate tissue compression kinematics, stepper motor and drive circuitry, linear actuator and associated hardware.

C. Precision Distance Measuring Unit - comprising, for example, linear variable differential transformer (LVDT), driving circuitry and mounting hardware.

D. Data Collection and Conditioning Unit - comprising, for example, a personal computer with multichannel analog to digital board for data filtering, amplification, conditioning for display, and storage.

E. Power Supply - to provide electrical power for driving electrical circuits and the stepper motor.

Optionally, a Force Measurement Unit - strain gauges and bridge circuitry mounted to mechanical linkages for measuring tissue compressive forces and mechanical linkage deformations.

These components are next described in greater detail.

The noninvasive device to determine THb and Hct values based on the photometric methods explained above comprises five subunits with an optical sixth subunit. The first is the photometric subunit comprised of, for example, a near isobestic point (810 nm) communications type laser diode (LT010MF, Sharp Corp., Osaka, Japan) with control circuitry (IR3C01 Sharp Corp., Osaka, Japan), or like light source capable of emitting light of the desired wavelength for a given chromophore to be measured, an integrated photodiode and amplifier circuit chip with signal conditioning circuitry (e.g., OPT201, Burr-Brown Corporation, Tucson, AZ) and mounting hardware. Light sources capable of creating a radiant energy source of wavelengths up to 11,000 nm are known in the art.

The tissue compression subunit comprises a four bar mechanical linkage for effecting tissue compression kinematics. The opposing arms of this subunit move together along nearly parallel

paths. This linkage may be driven manually or by stepper motor with linear actuator (e.g., motor model P310.158 and linear gear box model L10.100.01, Portescap US, Inc., 36 Central Ave., Hauppauge, NY) hardware and control circuitry.

The precision distance measurement subunit comprises, for example, a linear differential variable transformer (LVDT) (model S300, Columbia Research Labs, Inc., 1925 MacDade Blvd., Woodlyn, PA 19094) with the core mounted to one arm of the tissue compression subunit and the transformer primary and secondary windings to the other arm and control circuitry. However, any means for precisely measuring the comparison distance would be acceptable.

Among the variables to be assimilated by the data collection and conditioning unit are the measurements of initial tissue thickness, tissue compression distance, photodiode signal strengths, tissue compression forces and time of compression. Time of compression is potentially important because non-blood tissue fluids are somewhat mobile, but not nearly so mobile as blood. In addition to measuring the necessary elements, it would also be desirable for the data collection unit for perform the necessary calculations as described above to provide a continuous readout of blood constituents.

A power supply subunit powers all the electronic signal conditioning circuits and drives the laser diode and the stepper motor. The data collection subunit may comprise, for example, a Gateway2000 80486-based personal computer (Gateway2000, 610 Gateway drive, North Sioux City, SD) equipped with a 12 bit multichannel analog to digital converter board (model Dt2814, Data Translation, Inc., 100 Locke Drive, Marlborough, MA 01752) for acquiring signals.

Additionally, a force measurement subunit may optionally be provided to measure compression forces and to allow monitoring at mechanical arm deformations upon actuation of the tissue compression unit. The force measurement subunit can be incorporated so as to act as a safety interlock, interrupting power to the tissue compression unit as soon as a pre-set limit is exceeded. The force measurement subunit also enables an operator of the device to enter calibration corrections to account for such known individual variable such as elevated blood pressure which may otherwise provide for an undesirable bias in the collected data.

Although the strength of light measured through the tissue from the laser diode source is generally quite strong, there is a potential for error being introduced from ambient light levels. This is also a problem with pulse oximetry that is usually handled by "chopping" the light source (i.e., cycling them rapidly on and off) so that ambient light levels may be measured during off period. The ambient light levels are then subtracted from the light levels with the laser diode to obtain a value that does not include the ambient light. Since the laser diode selected was designated for communications use, it is capable of operation from DC to hundreds of megahertz.

According to the foregoing description, one simple embodiment of this invention is shown schematically in Figure 5. The laser diode 1 and photodiode 2 forming the photometric unit are mounted behind glass, which may include polarizing filter, directly on the calipers of a micrometer. Thus, the photometric unit is integral to the tissue compression unit, which in this case requires no stepper motor. The precision distance measuring unit 3 is provided by the readout from the micrometer as the opposing jaws of the micrometer are used to compress an illuminated body part placed between the opposing jaws of the micrometer.

A data collection unit 4, comprising a signal conditioning (amplification and filtering) and a separate display unit, provides a readout of the light intensity produced by the laser diode 1 and the amount of light received by the photodiode 2. The power supply is shown as 5.

In a different embodiment of this invention, shown in Figure 7, there is provided a source of radiant energy 1, a receiver of radiant energy 2, comprising the photometric unit. Once again, the photometric unit is integral to the tissue compression unit, which further comprises a motorized pump platform 6 and a motor driven screw 7, for achieving precise compression of a tissue placed between the light source 1 and receiver 2. The precise amount of compression produced by action of the motorized compression unit provided a precisely measured amount of linear distance change between the light source 1 and detector 2, and this information is fed directly to a multi-channel data acquisition and controller system 4. Thus, the tissue compression unit and precise distance measuring unit 3 of the invention are, in this embodiment of the invention, integral to each other.

A power source 5 is indicated, and the data collection unit 4 is exemplified as a two component unit comprising a multi-channel data acquisition and controller system and a personal computer which is capable of performing all the necessary calculations of light intensities detected and change in optical length to provide a continuous readout for any given wavelength/blood component. In addition, force measurement unit 8 comprising a pressure transducer, is provided and can act as a power interrupt (interlock) to stop tissue compression if a pre-set pressure limit is exceeded.

As an additional embodiment of a data collection device, Figure 9 exemplifies a preferred embodiment. The radiant energy source (e.g., a laser diode) 1 and detector 2 are shown on opposing arms of the device, thereby forming an integral photometric unit/tissue compression unit. The tissue compression unit is actuated by a stepper motor 9, which transmits tissue compression pressure to the photometric unit. The amount of compression is measured by a linear variable differential transformer (LVDT) 3 which acts as the precision distance measuring unit. For simplicity of representation, the power supply, which energizes the stepper motor, the LVDT, and the photometric

unit, is not shown. Strain gauges are provided as the force measurement unit with the previously described function of tissue compression interrupt.

The foregoing principles and device were tested and *in vivo* data gathered as further reported below in Example 17.

Following are examples which illustrate procedures, including the best mode, for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

Example 1

The invention claimed here can be practiced with only one light source and a means of ΔV determination. Access to SpO_2 output (obtained from any accurate source, such as a pulse oximeter) is required to calculate either THb and Hct, or CaO_2, depending upon the algorithm chosen. In one embodiment, the novel device can be built into a pulse oximeter; no additional light source is required. The component that determines ΔV is also supplied. The measurement of changes in $mHbO_2$ is then correlated to volume changes that are either passively measured or actively produced.

Example 2

Changes in the mass of oxyhemoglobin, total hemoglobin, and reduced hemoglobin molecules can be measured via absorption photometry using light having a wavelength from between about 400 nm and about 1100 nm. Other blood components may be measured using wavelengths up to and including 11,000 nm. For example, a wavelength of about 660 nm can be used for direct HbO_2 measurement (Figure 2). Other wavelengths which can be utilized include 810 nm (direct THb determination, see Figure 3) and 940 nm (direct RHb measurement). These wavelengths of light are sensitive to changes in $mHbO_2$, mTHb, and mRHb, respectively.

The corrected AC signal can be extracted from a standard pulse oximeter. Alternatively, such a corrected AC signal could be readily obtained by a person skilled in the art utilizing standard equipment and photometric procedures. However, correction of the AC signal is not necessary in all applications. The AC or DC signal can be used in the algorithm where THb is measured directly (Figure 4) using 810 nm light.

The desired DC or AC signal is then used to calculate $\Delta mHbO_2$. In the embodiment where $mHbO_2$ is measured directly, for example, this can be done by generating a calibration curve which relates change of $mHbO_2$ to changes in 660 nm corrected AC signal amplitude. $\Delta mHbO_2$ can be

determined indirectly with the DC signal from an 810 nm light source. THb is measured directly and with SpO_2, $\Delta mHbO_2$ is then calculated using equation (2).

There are a number of commercially available pulse oximeters which are capable of supplying the desired AC and/or DC signal. Additionally, these devices can be used to obtain accurate SpO_2 input values. For example, the Nellcor N-100 (Nellcor, Inc., Hayward, CA) and Ohmeda 3700 (Ohmeda, Boulder, CO) pulse oximeters are accurate to within 7% of their displayed saturations (Cecil, W.T., K.J. Thorpe, E.E. Fibuch, and G.F. Tuohy [1988] J. Clin. Monit. 4(1):31-36). The Datascope ACCUSAT (Datascope Corp., Paramus, NJ) and the Ohmeda 3700 pulse oximeters display saturation within 2.4% of actual SaO_2 (Mendelson, Y. J.C. Kent, A. Shahnarian, G.W. Welch, and R.M. Giasi [1988] J. Clin. Monit. 4(1):59-63). Regression analysis shows these products have high correlation coefficients with small standard error of estimate (r=0.99, SEE=1.29% and r=0.99, SEE=1.72% for the Datascope ACCUSAT and Ohmeda 3700, respectively).

Example 3

Although only a single light source is needed in most adult patients, more than a single light source can also be employed. Indeed, additional light sources may be useful in determining CaO_2 in circumstances where other light-absorbing hemoglobin species are present.

Measurement of other light-absorbing blood constituents may also require additional light sources to optimize the measurement accuracy. Determination of the proper wavelength to be used for measuring various blood constituents is within the skill of those trained in this field.

Example 4

Any type of energy which can be measured and used to quantitate blood constituents may be used to practice the subject invention. Thus, any form of electromagnetic radiation, sound wave, or magnetic property which can be used to trans-irradiate a body part can be utilized so long as the characteristics of the energy are altered by the relevant blood constituents and so long as these changes can be measured and correlated with changes in blood volume.

Furthermore, it is not critical that the energy be externally supplied. By measuring energetic and/or magnetic properties emitted from the tissue itself, it is possible to practice the invention. For example, by analyzing the magnetic properties attributable to the iron associated with hemoglobin and correlating these properties with changes in the blood volume, the relevant blood constituents can theoretically be quantified.

Example 5

It is possible to measure volume changes directly using volume or pressure transduction. For example, a noninvasive blood pressure (NIBP) monitor generates an arterial pressure wave form using an air filled bladder around the finger. This commercially available device rapidly pressurizes and depressurizes the bladder to maintain the finger surrounded by the bladder at nearly constant volume during the pulse. The pressure changes in the bladder can be correlated to volume changes in the finger utilizing standard gas law calculations. These calculations take into account original bladder volume, gas temperature, change in bladder volume and compliance of the bladder.

Example 6

A second approach for determining volume changes is to measure changes in the length of the light path between the light source and photodetector. Then the volume is approximated by modelling the light path. For example, this model can be a cylinder between emitter and detector with a cross-sectional area equal to the receptive field of the photodetector. When the length of this cylinder changes, such as occurs during pulsatile blood flow, the new volume and, hence, the volume change, are easily determined.

A variety of devices exist that transduce length with high precision. Sonomicrometers, strain gauges, Hall-effect transducers, optical interferometry, and electromagnetic field changes can all be utilized to measure small changes in length. Light intensity itself and light phase changes can also be used to measure distance changes.

Example 7

Measurements or changes in volume can be made passively or actively. Passive measurement would involve, for example, measuring the actual finger expansion and contraction with each pulse. We have been able to show that finger volume does change with each pulse. The finger was placed into a closed rigid chamber (syringe plunger port) filled with an incompressible fluid (water). A pressure transducer (Datascope P3 Module interfaced with a Datascope 870 Monitor, Datascope Corp., Paramus, NJ) was primed with water and connected to the syringe tip. A pulsatile pressure wave form was obtained and reproduced. This provides evidence that the finger does indeed experience volume changes with blood pulsation.

This experiment also demonstrates the feasibility of one method of volume change determination. If the pulse amplitude, original finger volume, original chamber size, and compliance of the rigid vessel are known, the volume change in the finger can be determined. This change can be used to calculate the volume change between the LED and photodetector.

Example 8

Measurement of actively produced volume changes can also be utilized. Active measurement results from compression and release of tissue at the measurement site by a known distance. If the light source and the photodetector are brought closer together by an external force, e.g., a motor, which produces a volume change in the receptive field, the same data can be obtained. This method requires some amount of HbO_2 to be displaced from the receptive field.

This procedure can result in the measurement of larger changes in volume compared to passive measurements of volume change during a pulse. Measuring larger volume changes can advantageously reduce experimental error during measurement.

Example 9

The device and method of the subject invention can be utilized in conjunction with life support systems and other medical instrumentations. For example, the subject invention can be used as a sensor for a continuous automatic feedback loop that is designed to maintain CaO_2 and/or THb or Hct. An infusion pump, ventilator, and/or anesthesia machine can be controlled by the sensor. The sensor would enable the system to maintain levels of CaO_2 and/or THb/Hct at levels which are predetermined by the operator of the system.

Example 10

The wavelength and source of light employed in the design of the invention can be optimized by those skilled in the art, depending on the particular application. Thus, if direct $mHbO_2$ determination is desired, an approximately 660 nm light source can be utilized. If, however, direct mTHb determination is desired, a wavelength near the isobestic point of 805 nm (e.g., 810 nm) can be employed. If direct determination of RHb is sought, a light wavelength near 940 nm can be used. With any of these wavelengths, the remaining unknown parameters (THb and/or Hct and/or RHb and/or CaO_2) can be determined indirectly with the addition of an accurate SpO_2 value using the various formulae discussed above.

Furthermore, the light can be from an LED and/or laser source, such as a laser diode. The laser offers advantages over an LED because its emission spectra is much narrower, its power attenuation with increasing distance is small in comparison, its output is more directional and it is a more ideal beam. Thus, reproducibility and confidence are improved. These advantages allow for easier modeling and subsequent implementation of applications where the distance between light source and receiver changes.

If a laser or other light emitting source is utilized, the use of fiber-optic technology may also be employed. Fiber-optic cables allow the somewhat motion-, temperature-, and current-sensitive laser or other light emitting source and detector elements to remain protected and remote from the patient, and also provide an extremely high degree of electrical isolation between the patient and the device.

Example 11

Noise consists of the background light that enters the photovoltaic cell (PVC) and alters the signal output. Polarizing films can be employed to reduce the effects of background scattered light. This is achieved by placing a polarizing film in a known orientation between the emitter and tissue and another film in an identical orientation between the tissue and receiver. This configuration prevents randomly polarized light from entering the PVC. As a consequence, scattered light from the emitter, as well as ambient light that is rotated with respect to the orientation of the polarizing film, is filtered from the PVC input. All photoplethysmographic devices, including pulse oximeters, would benefit from this application.

The use of polarizing films in this fashion has the added advantage of essentially defining a volume of tissues of similar cross-sectional area to the PVC. The volume's length is the linear distance between emitter and detector. Hence, volume determination is simplified.

Example 12

"Active" volume determination requires a physical displacement of the emitter relative to the PVC. This displacement can be mechanically limited to a known distance. It can also be limited by the tissue pressure upon one of the device elements (i.e., the PVC or light source), or by a combination of pressure and displacement.

Example 13

Light near the isobestic point of HbO_2 and RHb (e.g., 810 nm) is absorbed essentially equally well by both species. Therefore, an AC signal representative of pulsatile arterial blood and a DC signal representative of both arterial and venous blood can be obtained. Since arterial and venous THb are the same, either the AC or DC signal can be utilized to determine THb. Input of SpO_2 (which reflects arterial oxygen saturation) then allows arterial oxygen content (CaO_2) to be calculated. If a DC signal is also obtained at 660 nm, a total (i.e., combined) arterial and venous

oxygen content ($CavO_2$) can be determined. Venous O_2 content (CvO_2) can then be calculated by subtracting CaO_2 from $CavO_2$. If one integrates over time (CaO_2-CvO_2), one can determine local O_2 consumption.

Example 14

The method of actively varying volume can be applied equally well to the new pulse oximeter technologies that employ reflectance or backscatter of light for their signals. If one varied the slab length, width, or depth from which they receive their signals, essentially a volume change would have been made and similar algorithms to those described above would apply. Therefore, SpO_2, THb, HbO_2, RHb, CaO_2 and local oxygen consumption could each be determined using these new technologies.

Example 15

The claimed device can also be used to determine interstitial fluid content, or state of hydration. Currently, there is no device which can quantitatively measure a patient's hydration status. Such a device would be beneficial in the clinical assessment of delirium, hypotension, tachycardia, and other medical conditions. Thus, it could be used in critical care settings (e.g., emergency rooms) and in chronic care settings (e.g., nursing homes).

The novel device of the subject invention operates by measuring changes in signal strength that occur after a rapid compression (or decompression) of a tissue. The tissue can be thought of as a two compartment system: the intravascular compartment that contains blood and the interstitial compartment that contains body water. By externally deforming the tissue, a hydrostatic pressure change is applied. Since the fluid cannot shift instantaneously between compartments, it shifts first within the compartment with the least resistance to flow. The interstitial fluid is impeded from making rapid shifts because it is trapped in tissue planes and held within the interstitial compartment by hydrophilic molecules. The blood within the intravascular compartment, however, is capable of making rapid shifts. Thus, upon rapid compression, blood would leave the compressed site almost immediately, and only subsequently does the interstitial water begin to leave the compressed region. Likewise, if the tissue was rapidly decompressed, blood would almost immediately refill the vasculature. Following this, the water would refill the interstitial compartment. The rate at which these shifts occur can be used as an indication of hydration status for any given blood pressure.

The measured signal varies with the mass of absorber (i.e., mass of HbO_2, RHb, or THb, depending on the wavelength used) in the light path. As reasoned above, after rapid (de)compression, the signal can be expected to vary in a fashion that is related to hydration status.

Example 16

It is possible to combine any of the various applications into a new application. For example, a backscatter oximeter may be used to determine mixed venous O_2 content in the superficial jugular vein while CaO_2 is determined at a peripheral site. Such a combination may provide a good solution to the Fick equation for cardiac output. Another example of a new application is to combine the algorithms that directly determine mTHb and $mHbO_2$ by the new method and design an entirely new pulse oximeter based on measuring vascular volume changes.

Example 17

Living tissue is not the ideal medium for application of the Beer-Lambert law (it is not uniform and scatters light as well as absorbs it). Ultimately, whether the tissue compression method works in practice must be determined empirically. To verify the method, both animal and human studies were performed.

a. Dog Study

In this study, we used a well collimated laser diode (LT010MF, Sharp Corp., Osaka, Japan) with a wavelength of 810 nm. As shown in Figure 5, we mounted the laser diode behind a glass slide on one arm of a pair of calipers. On the other arm we mounted a photodiode behind another glass slide. The laser diode module included a control chip (IR3C01 Sharp Corp., Osaka, Japan) to maintain stable power output. The photodiode signal was transmitted by shielded cable to a signal conditioning unit for current to voltage conversion, amplification and filtering. The signal amplitude was then read off from a digital volt meter.

A mongrel dog was anesthetized with a barbiturate infusion. Data were collected by placing the dog's tongue between the glass slides of the caliper assembly and observing voltage readings with the tissue both uncompressed and compressed. A block of material was mounted on the caliper slide to determine caliper excursions during compression. THb values were incrementally lowered by intravenous administration of a 0.9% saline solution. After each administration of saline, blood was drawn and THb determined by CO-Oximeter (model IL-282, Instrument Laboratory, Lexington, MA). Photodiode signal measurements were taken with the tongue in uncompressed and compressed states. Typically, two to five uncompressed and compressed readings were taken for each THb measurement from the drawn blood. Figure 6 shows CO-Oximeter THb versus $\ln(I_1/I_2)/\Delta L_B$, which is the right hand side of (17) except for not including the constant K_{THb}. A good linear relation was observed ($R=0.95$) for a wide range of THb values (5.6 to 12.2 g/dL). Some of the variance in the data may be explained by the dog's vigorous diuresis that tended to increase THb with time, thus affecting later measurements taken after blood was drawn.

b. Human Volunteers Study

For the human study, we used the device shown in Figure 7. It was constructed from a motorized infusion pump. Again, the laser diode and the photodiode were mounted on opposing arms of the device, behind glass slides. The new device was used to compress finger tip tissue side-to-side and measure photodiode output. Data from five Caucasian and two African American volunteers were taken with tissue compression distances of 2.0 and 2.5 mm. THb values were determined from drawn blood samples by the CO-Oximeter as in the dog study.

These data were plotted after calculating $\ln(I_1/I_2)/\Delta L_B$, show a strong linear trend that is consistent across all the volunteers (R=0.85) (Figure 8). There is a certain amount of variance that would be expected in preliminary data.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

Claims

1. A device for noninvasively determining total hemoglobin, arterial oxygen content, and/or hematocrit in an animal or human, said device comprising a means for photometrically measuring changes in the mass of oxyhemoglobin, total hemoglobin, or reduced hemoglobin, wherein said changes in desired hemoglobin species correspond to measured or known changes in volume.

2. The device, according to claim 1 wherein said measurement of the changes in mass of the hemoglobin species is accomplished by a method comprising one of the following: 1) subjecting a portion of the body to an appropriate energy form and measurement of the attenuation of the energy resulting from the absorption of said energy by said body portion; and, 2) measurement of emitted energy from a body part.

3. The device, according to claim 2 wherein a body part is subjected to energy of a form selected from the group consisting of electromagnetic radiation and soumd waves.

4. The device, according to claim 3 wherein said energy form is electromagnetic radiation.

5. The device, according to claim 4, wherein said electromagnetic radiation is produced by a laser.

6. The device, according to claim 4, wherein polarizing film is used to reduce background noise and scattered light.

7. The device, according to claim 6, wherein a first polarizing film is placed between an electromagnetic radiation source and the body portion to be subjected to said radiation, and a second polarizing film is placed between the body portion subjected to said radiation and a device for measurement of the attenuation of said radiation, said polarizing films being aligned such that radiation emitted by the source and passing directly through said body portion will reach said measuring device.

8. The device, according to claim 7, wherein said electromagnetic radiation is produced by a laser.

9. The device, according to claim 4, wherein said appropriate energy form is light having a wavelength in the range from about 400 nm to about 1100 nm.

10. The device, according to claim 9, wherein said wavelength is selected from the group consisting of approximately 660 nm, approximately 810 nm, and approximately 940 nm.

11. The device, according to claim 7, wherein magnetic properties emitted by the body are measured.

12. The device, according to claim 1, wherein said volume change is actively induced by external means.

13. The device, according to claim 12, wherein said volume change is achieved by a mechanically limited and known change in length of a volume of known cross-sectional area.

14. The device, according to claim 1, wherein said volume change is measured by pressure transduction.

15. The device, according to claim 1, wherein said volume change is approximated by measuring changes in the length of a volume of known cross-sectional area.

16. The device, according to claim 15, wherein said length is measured by means selected from the group consisting of sonomicrometers, strain gauges, Hall-effect transducers, optical interferometry, and electromagnetic field changes.

17. The device, according to claim 1, wherein said volume change is determined by measuring the pulsatile pressure wave form obtained when a body part is immersed in an incompressible fluid.

18. The device, according to claim 17, wherein said incompressible fluid is water.

19. The device, according to claim 1, wherein said body part is selected from the group consisting of hands, fingers, feet, toes, ears, earlobes, nares, lips, and tongue, or any other body part that can be effectively trans-illuminated.

20. The device, according to claim 1, wherein a desired AC or DC signal is input from an oximeter.

21. The device, according to claim 1, further comprising means for photometrically quantifying additional light-absorbing blood components.

22. The device, according to claim 21, wherein said additional light-absorbing blood components are selected from the group consisting of MetHb and COHb.

23. A device for measuring a blood constituent which comprises:

a) a photometric unit comprising a source of radiant energy of known wavelength, between about 400 nm and 11,000 nm, and a detector capable of measuring radiant energy between about 400 nm and 11,000 nm, said source and said detector being adapted so as to permit the interposition of an animal or human body part therebetween such that said radiant energy emitted from said source must pass through said body part before impinging on said detector;

b) a tissue compression unit comprising a mechanical linkage for effecting a controlled amount of tissue compression, said tissue compression unit acting as a housing for said radiant energy source and said detector of (a), such that upon interposition of said body part, said tissue compression unit compresses said body part altering by a controllable amount the distance between said radiant energy source and said detector;

c) a precision distance measuring unit mounted on said tissue compression unit such that precise measurement of the amount of tissue compression is obtained upon actuation of said tissue compression unit;

d) a data collection and conditioning unit for collecting and processing data on the amount of distance varied by said tissue compression unit and the amount of radiant energy received by said detector of said photometric unit; and

e) a power supply to provide electrical power for driving the electrical circuits of the foregoing elements a-d.

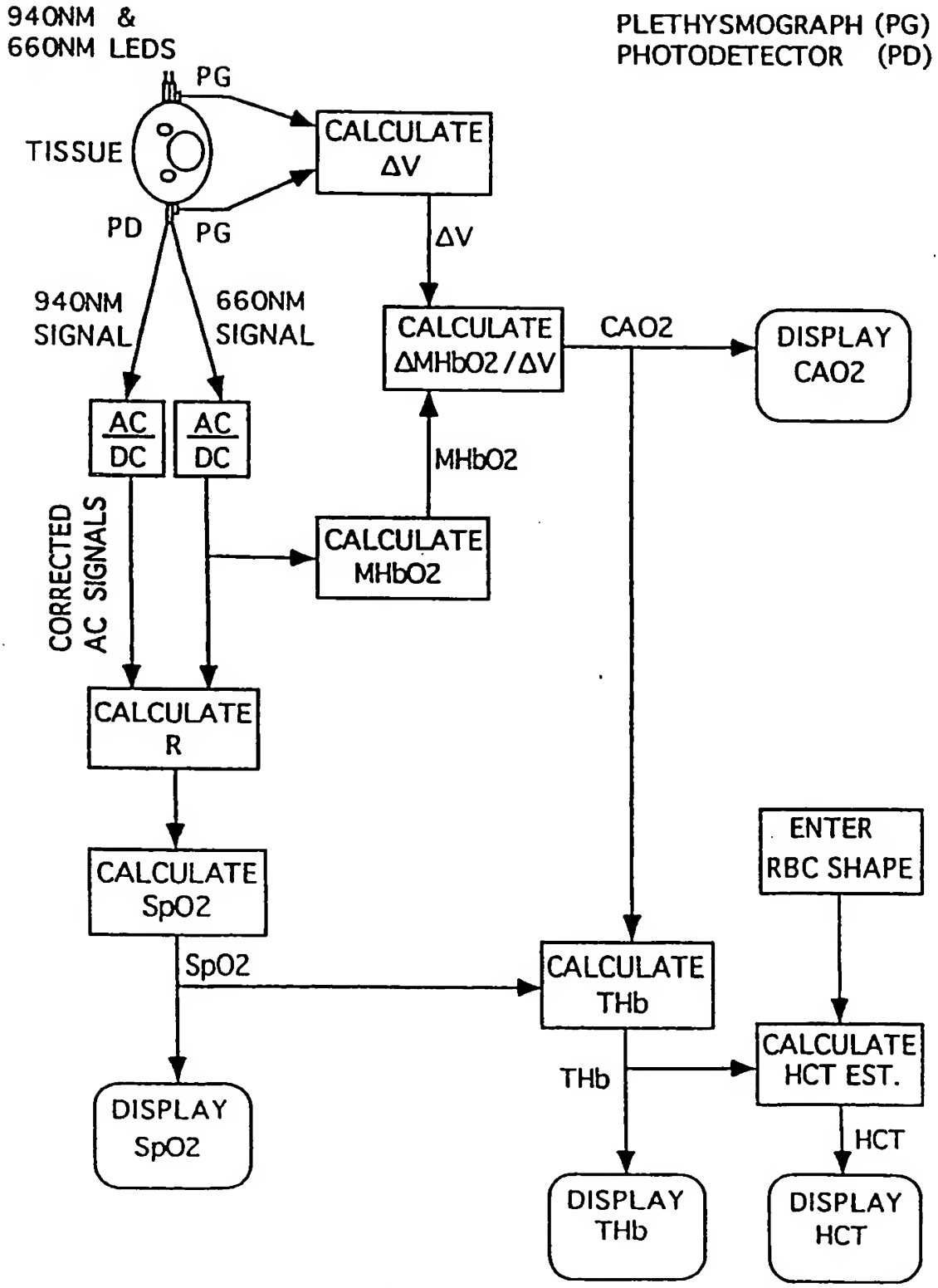
24. The device of claim 23 wherein said tissue compression unit additionally comprises a force measurement subunit to measure compression forces and to allow monitoring of mechanical arm deformations upon actuation of said tissue compression unit, said force measurement subunit acting as a safety interlock such that upon exceeding a pre-set limit, the force measurement subunit

interrupts power to the tissue compression unit, said force measurement subunit also providing the device operator with the option of entering calibration corrections for known individual characteristics such as elevated blood pressure, which may otherwise provide an undesirable bias to the collected data.

25. The device of claim 23 wherein, in addition to said data collection and conditioning unit, collecting and processing said data on the amount of distance varied by said tissue compression unit and the data from said photometric unit, said unit further performs the necessary calculations to provide a continuous readout for the given blood component being measured.

26. A non-invasive method for measuring blood hemoglobin, hematocrit, oxygen content, glucose, bilirubin, cholesterol or other blood components which comprises using the device of claim 25.

27. The method of claim 26 wherein a wavelength of 810 nm is used for measuring hemoglobin and a wavelength of 9700 nm is used for measuring blood glucose.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PLETHYSMOGRAPH (PG)
PHOTODETECTOR (PD)
PG
TISSUE
PD
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CALCULATE
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940NM
SIGNAL
660NM
SIGNAL
CALCULATE
ΔMHbO2 / ΔV
CAO2
DISPLAY
CAO2
AC
DC
AC
DC
MHbO2
CORRECTED
AC SIGNALS
CALCULATE
MHbO2
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SpO2
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DISPLAY
SpO2
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RBC SHAPE
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THb
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THb
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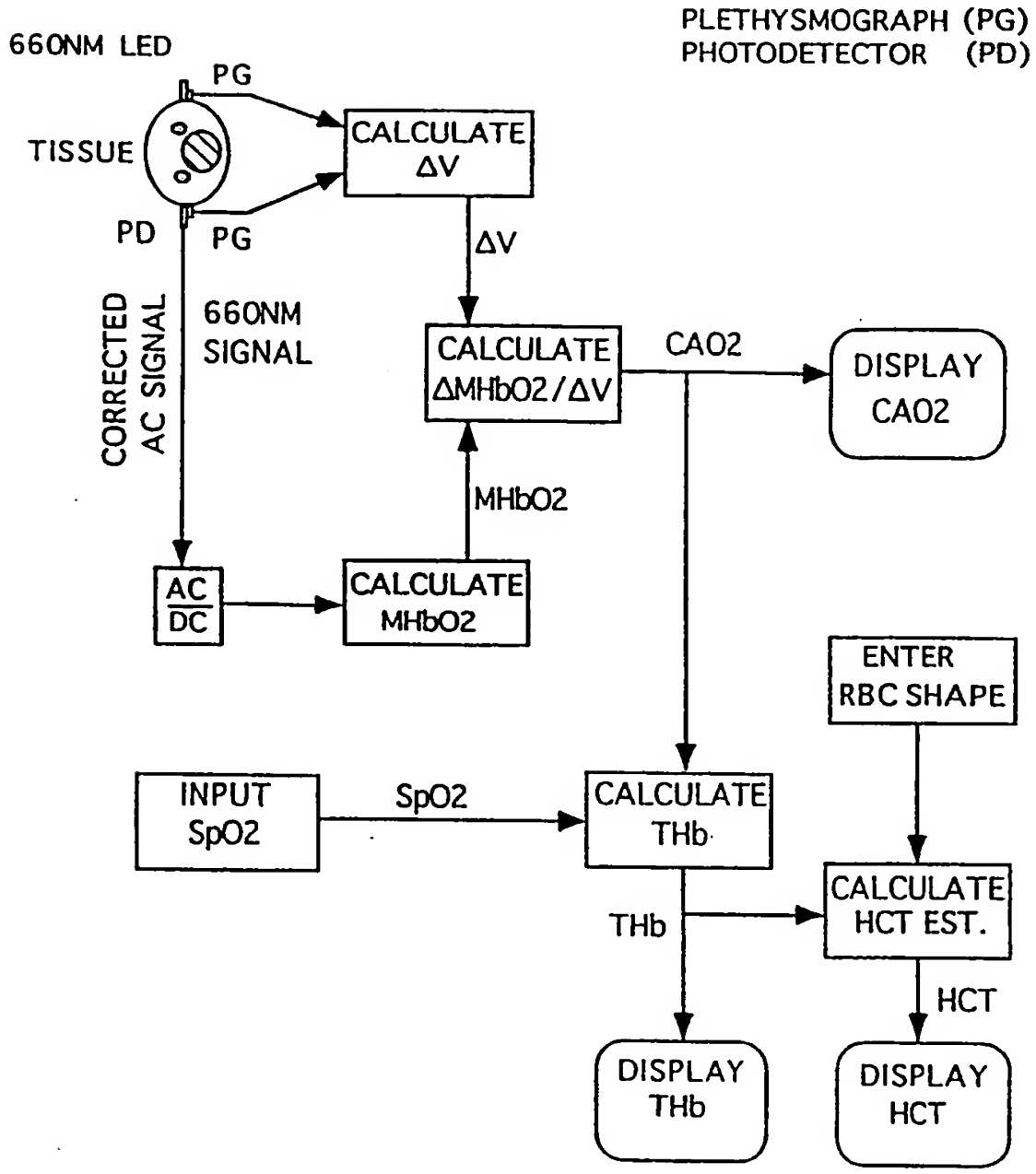
HCT

Figure 1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ΔV
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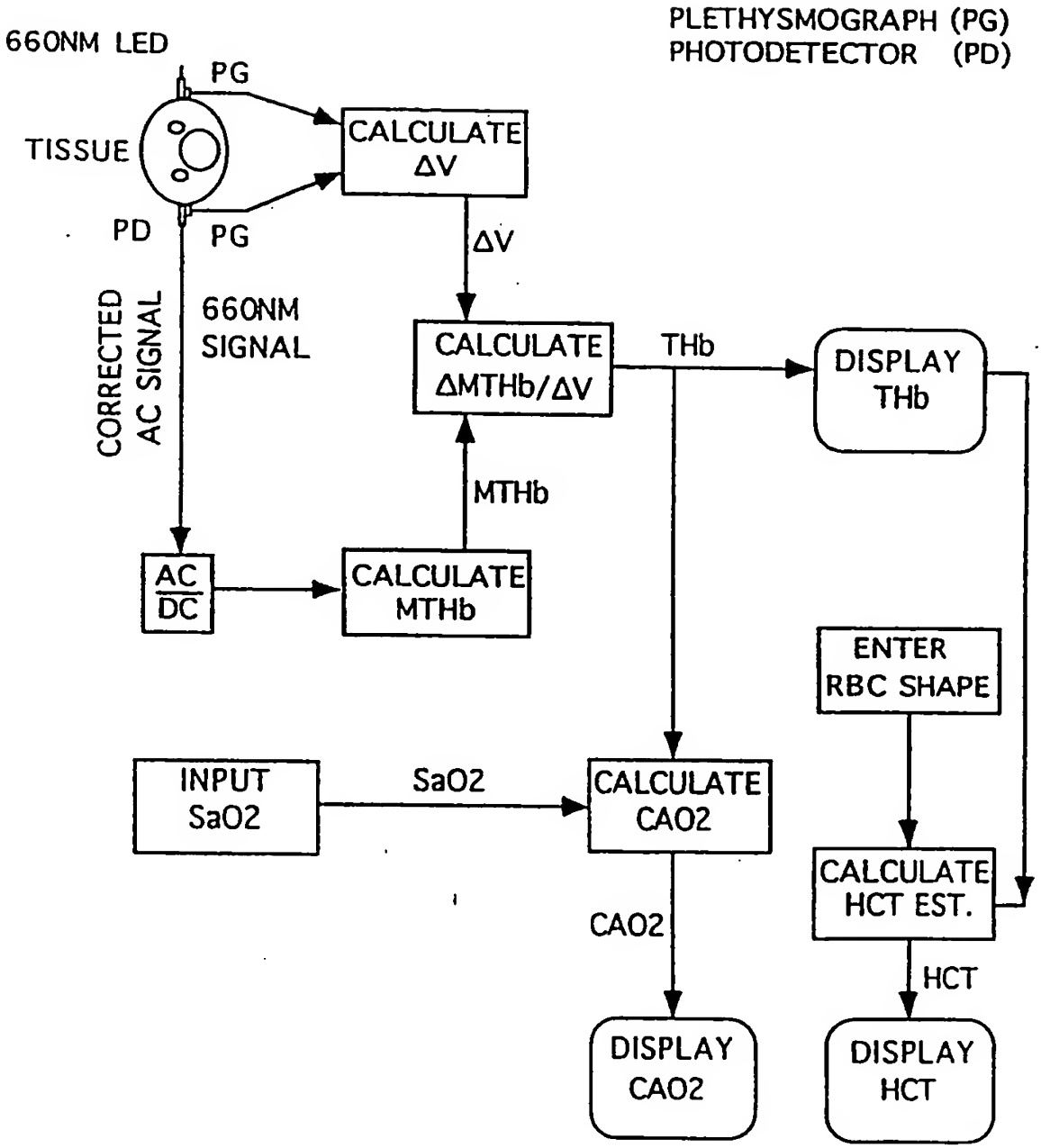
PHOTODETECTOR (PD)
CORRECTED AC SIGNAL
660NM SIGNAL
CALCULATE ΔMHbO2/ΔV
CAO2
DISPLAY CAO2
MHbO2
AC/DC
CALCULATE MHbO2
ENTER RBC SHAPE
INPUT SpO2
SpO2
CALCULATE THb
THb
CALCULATE HCT EST.
HCT
DISPLAY THb
DISPLAY HCT

Figure 2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ΔV
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CORRECTED AC SIGNAL
660NM SIGNAL
CALCULATE ΔMTHb/ΔV
THb
DISPLAY THb
MTHb
AC/DC
CALCULATE MTHb
ENTER RBC SHAPE
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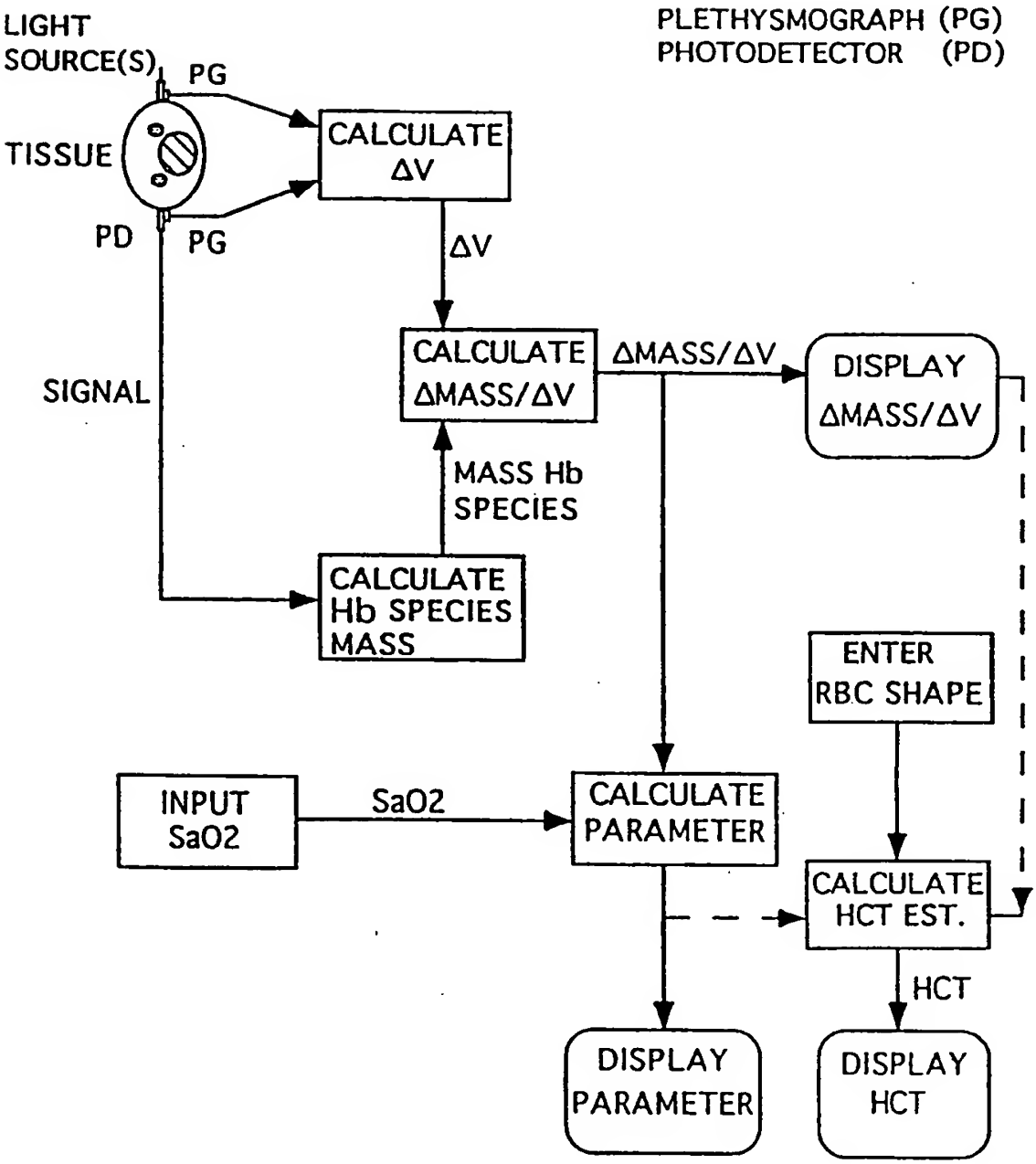
SaO2
CALCULATE CaO2
CALCULATE HCT EST.
CaO2
HCT
DISPLAY CaO2
DISPLAY HCT

Figure 3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ΔV
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CALCULATE ΔMASS/ΔV
ΔMASS/ΔV
DISPLAY ΔMASS/ΔV
MASS Hb SPECIES
CALCULATE Hb SPECIES MASS
ENTER RBC SHAPE
INPUT SaO2
SaO2
CALCULATE PARAMETER
CALCULATE HCT EST.
HCT
DISPLAY PARAMETER
DISPLAY HCT

Figure 4

Fig. 5

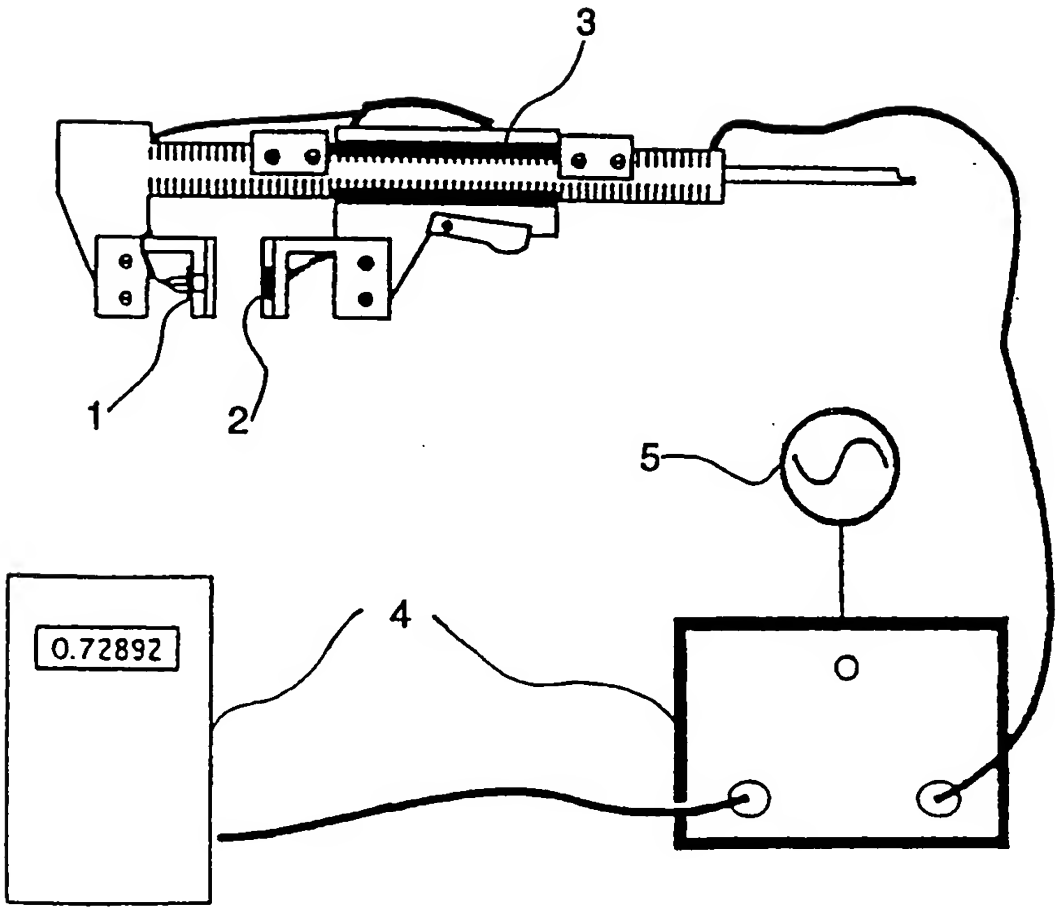


Fig. 6

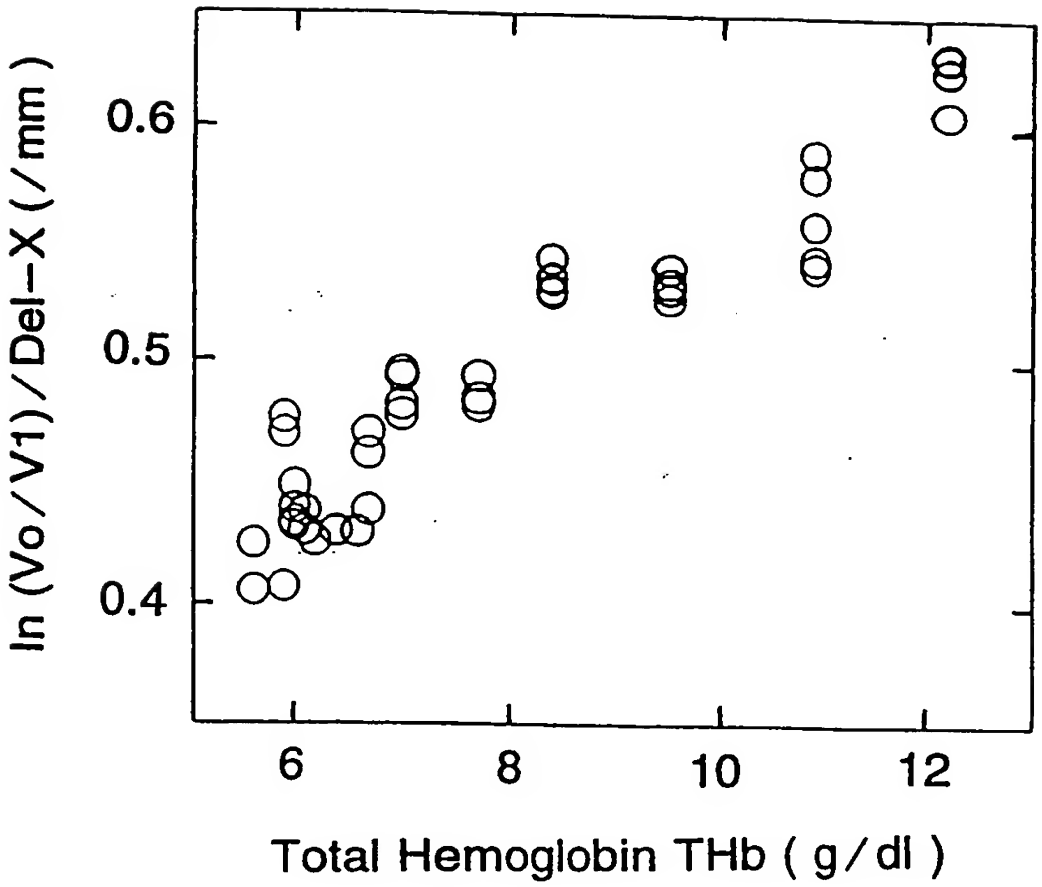


Fig. 7

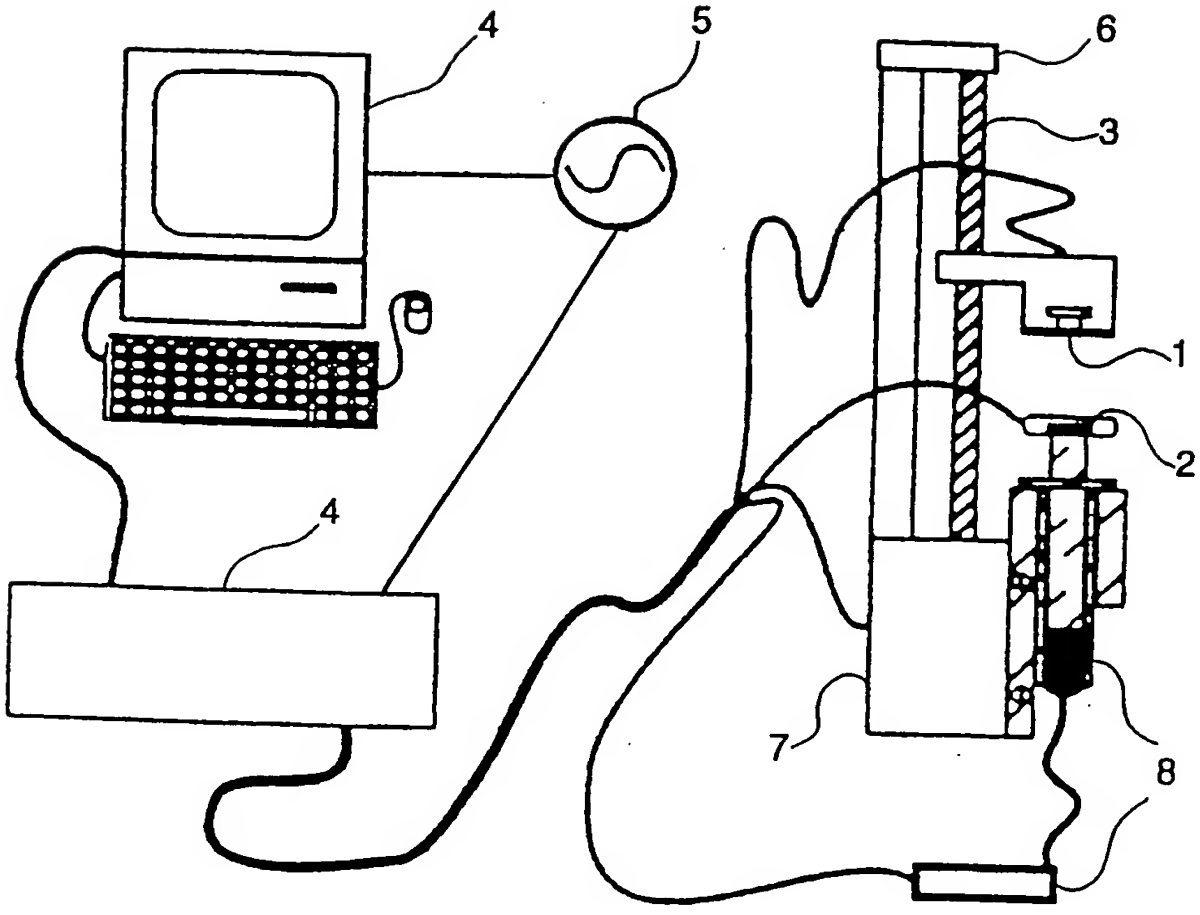


Fig. 8

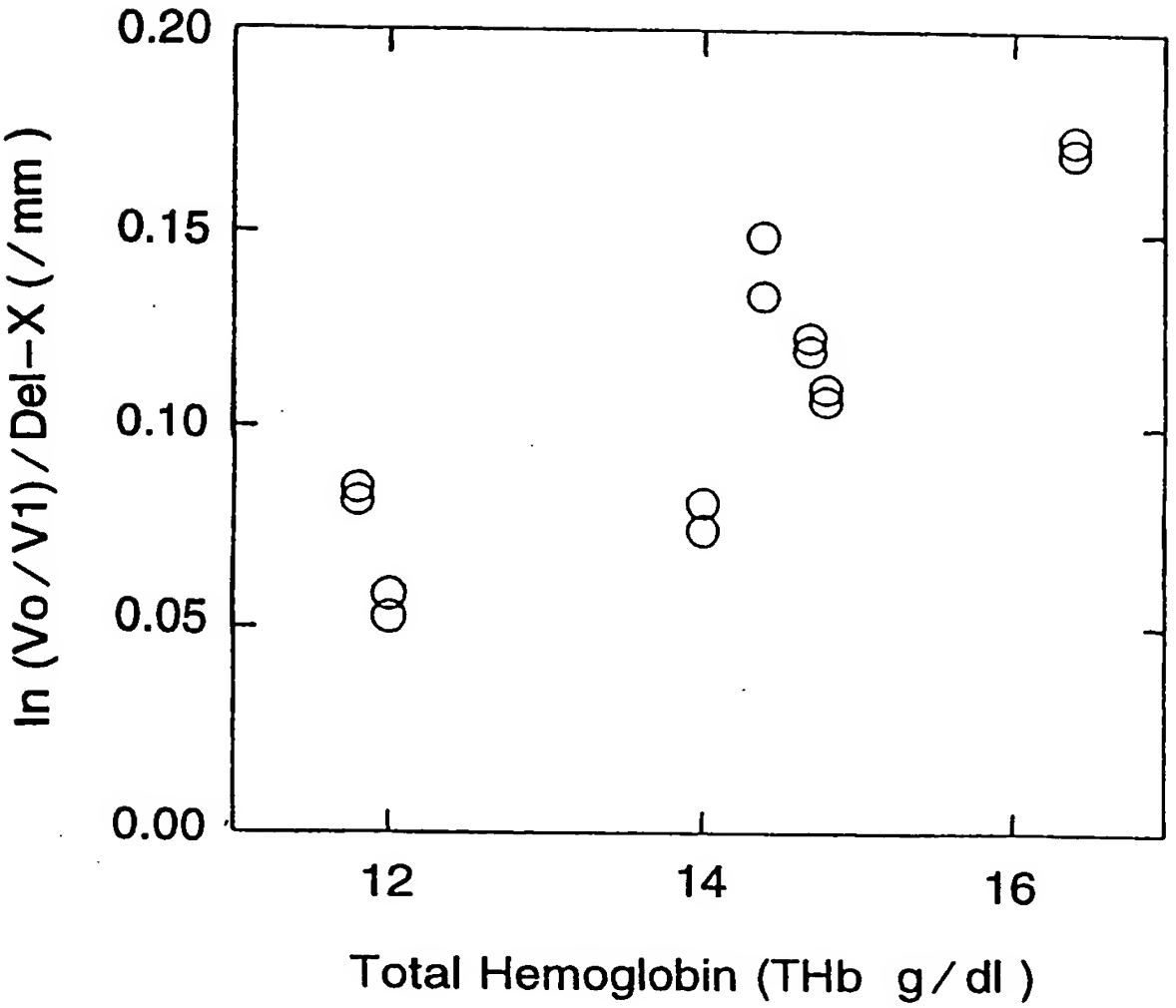
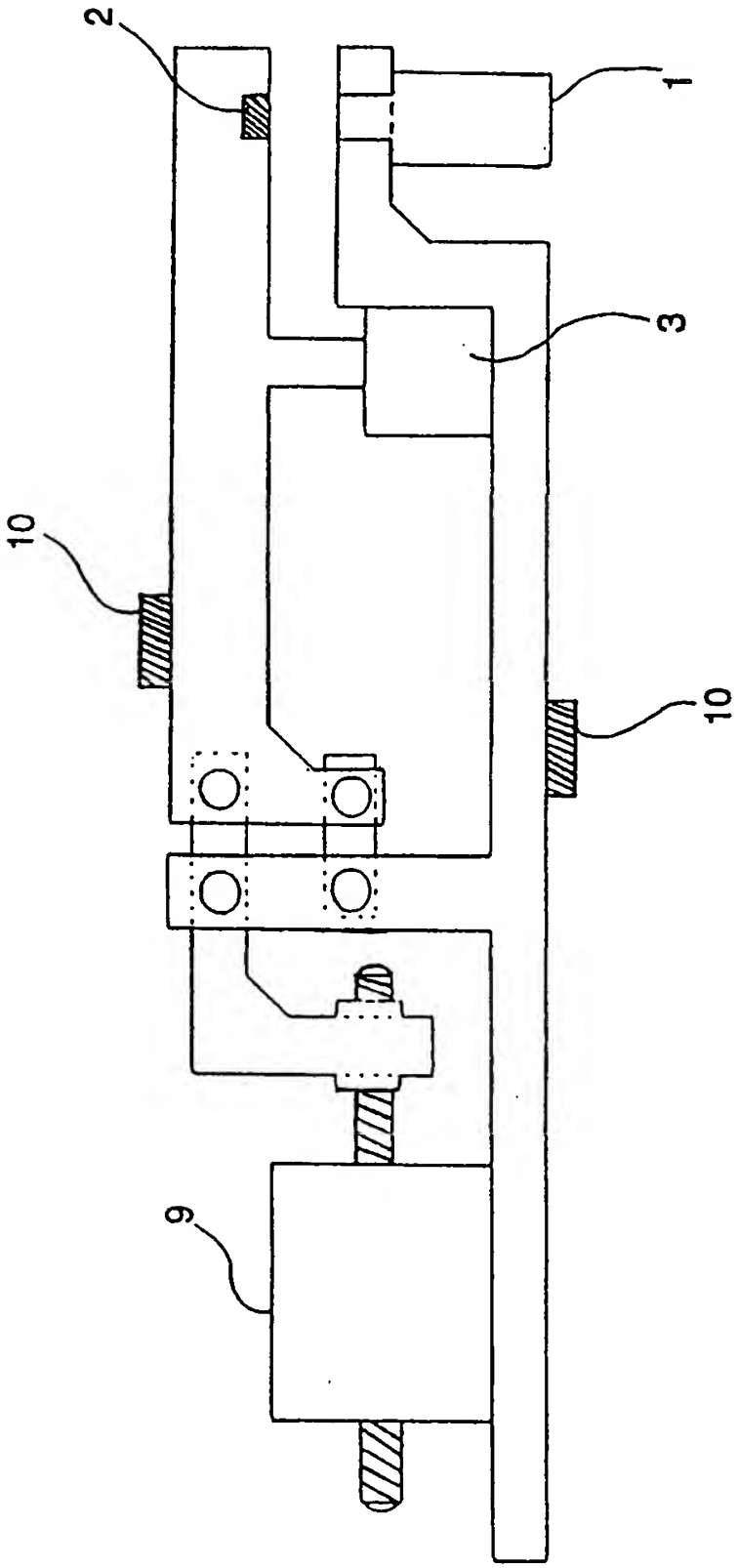

0.20
0.15
0.10
0.05
0.00
ln (Vo/V1)/Del-X (/mm)
12
14
16
Total Hemoglobin (THb g/dl)

Fig. 9



INTERNATIONAL SEARCH REPORT

Int[illegible]nal Application No
PCT/[illegible]96/09148

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO,A,90 04353 (GRAVENSTEIN & AL.) 3 May 1990 (& US 5101825 cited in the application) see the whole document	1-22 23-25
A	US,A,4 927 264 (SHIGA &AL) 22 May 1990 see the whole document	23-25
A	EP,A,0 619 981 (OHMEDA) 19 October 1994 see page 4, line 5 - line 8	27
A	WO,A,90 07905 (FUTREX) 26 July 1990 see page 15, line 5 - line 10	27
A	US,A,5 361 758 (HALL & AL.) 8 November 1994 see column 7, line 65 - column 8, line 6	26

☐ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 August 1996	26.08.96

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Lemercier, D

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/09148

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